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The Dutch Uniform Multicenter Registration System for Genetic Disorders and Malformation Syndromes

A. Monic N. Zwamborn-Hanssen,[1]* Jan B. Bijlsma,[2] Eric F.A.M. Hennekam,[2] Dick Lindhout,[4] Frits A. Beemer,[2] Egbert Bakker,[5] Wim J. Kleijer,[4] Henny F. de France,[2] Christine E.M. de Die-Smulders,[1] Martinus Duran,[2] Albert H. van Gennip,[6] J. Theo van Mens,[3] Peter L. Pearson,[2] Gerrit Mantel,[5] Rob E. Verhage,[4] and Joep P.M. Geraedts[1]

[1]Clinical Genetics Center Limburg, Maastricht, The Netherlands
[2]Clinical Genetics Center Utrecht, The Netherlands
[3]S.I.G., Utrecht, The Netherlands
[4]Clinical Genetics Center Rotterdam, Rotterdam, The Netherlands
[5]Clinical Genetics Center Leiden, Leiden, The Netherlands
[6]Clinical Genetics Center Amsterdam, Amsterdam, The Netherlands

In medical genetics, several systems are used to classify and code genetic disorders for the purpose of automated registration. In the Netherlands, a genetic diagnosis code system has been developed that links a unique four-digit code to a principal description and all current synonyms. The main goal of this coding system is to enable nationwide uniformity of coding, without losing access to information stored in the past, identified by the ICD/BPA code (the International Classification of Diseases as adapted by the British Paediatric Association) and/or the MIM code (McKusick's classification in Mendelian Inheritance in Man). To this effect, the Dutch diagnosis code is cross-referenced with the 2 pre-existing classification systems. Developments in medical genetics make regular updates of all coding systems necessary. In the Netherlands, new diagnosis codes are assigned centrally to preserve uniformity and distributed periodically to all 8 clinical genetic centers. Diagnosis codes are assigned in numerical order of inclusion, enabling quick and easy updates. It is possible to include subclassifications of disorders according to pattern of inheritance, gene location, and gene mutations and to cover all disorders and disorder subtypes which are not clearly distinguished by the 2 pre-existing classification systems. The architecture of the coding system is suitable for international use. It offers a practical solution for clinical geneticists in need of a coding system suitable for clinical use. The use of the diagnosis code will also facilitate reliable comparison of data and nationwide genetic epidemiological studies. Am. J. Med. Genet. 70:444–447, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: Dutch uniform diagnosis registration; genetic diagnosis; diagnosis coding system

INTRODUCTION

Since 1987, the 8 clinical genetic centers in the Netherlands (located in Amsterdam (2), Groningen, Leiden, Maastricht, Nijmegen, Rotterdam, and Utrecht) have been cooperating under one umbrella, the organization for the Automation of Clinical Genetic Registration (SAKGER). One of the aims of this collaboration was the development of a Dutch nationwide registration system that was compatible with, but gave improved discrimination above, the previously applied registration through the ICD/BPA and/or the MIM code (both described in more detail below). To this effect a new coding system has been developed. This diagnosis code is cross-referenced with the ICD/BPA and the MIM classification systems. In addition, the new system is more adaptable to the rapidly developing field of genetic subclassification, as will be explained.

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*Correspondence to: A. Monic N. Zwamborn-Hanssen, M.D., Clinical Genetics Center Limburg, P.O. Box 1475, 6201 BL Maastricht, The Netherlands.

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ICD/BPA Classification

In 1977, the World Health Organization issued the 9th edition of the International Classification of Diseases [ICD; World Health Organization, 1977], which is based on the organ system involved. A 3-digit number is used to indicate groups, extended by a dot and a fourth digit intended for subclassification into smaller categories and individual disorders. This classification leaves some rather large groups of heterogeneous disorders with the same code. It was left to the users of the classification to further subdivide these categories by additional digits if required. This was bound to lead to individuality of subclassification and hence to loss of uniformity. In 1979, the British Paediatric Association [1979] introduced a further subclassification (ICD/BPA) by adding a fifth digit (a second digit behind the dot). This subdivision was useful for coding congenital and perinatal disorders in particular and proved helpful to clinical geneticists. Even so, the subdivision of this single organ-based ICD/BPA classification system proved insufficient for systemic and metabolic disorders and especially for malformation syndromes, which frequently involve many different organ systems and can only be classified in residual groups.

McKusick's MIM Classification

In 1962, McKusick published a catalogue on X-linked traits. In 1966, the first edition was published of *Mendelian Inheritance in Man* [MIM; McKusick, 1966], the now classical reference catalogue on all traits with monogenic inheritance. Since then, many developments in the field of medical genetics have made constant updating and regular publication of new editions necessary, on an average of a new edition every 2 years. The most recent hard copy edition of MIM [McKusick et al., 1994] is an extensive and thorough reference book consisting of 2 volumes which is available on CD-ROM. There is also a network version (OMIM), which is updated daily and is available on the world wide web (http://www3.ncbi.nlm.nih.gov/omim). The disorders and traits listed in MIM are divided into 5 main categories: autosomal dominant, autosomal recessive, X-chromosomal, Y-chromosomal, and mitochondrial. Every entry has a 6-digit code with the first digit indicating the category. Allelic variants or defined genetic mutations have been assigned a 4-digit number following the primary entry number and a decimal point. The subclassification of every category is arranged, for the most part, alphabetically, according to the first or principal description chosen. Synonyms are given between brackets. The main disadvantage of this classification system is that it cannot be used easily for chromosomal and multifactorially inherited disorders, or multiple congenital anomaly syndromes of unknown or exogenous cause. Another problem is that different clinical entities are frequently retained within the same entry, if they are caused by mutations within the same structural gene. OMIM provides a sixth category, for genes which have not yet been associated with genetic diseases. This category is of no importance for genetic diagnosis registration.

In essence, the (O)MIM catalogue is gene centric and provides inadequate distinction for clinical phenotype variations and nonmendelian modes of inheritance, including imprinting phenomena. The introduction of the mitochondrial section has made an improvement but it belies the general title of the catalogue of *Mendelian Inheritance in Man.*

THE UNIFORM GENETIC DIAGNOSIS CODE

The Dutch coding system provides every diagnosis with a unique 4-digit code, which is assigned in order of inclusion (Table I illustrates this random assignment). Every code is linked to a principal description of a diagnosis and all current synonyms. Furthermore, every code is linked to one matching ICD/BPA code. A MIM code is only provided for those disorders which have the monogenic mode of inheritance described in MIM. Unlike the other 2 systems, the Dutch codes contain no hierarchical information, the only requisite being that they are unique.

Because concepts in medical genetics are constantly influenced by new developments, the list of codes has to be updated almost continuously. To preserve intrinsic hierarchy and uniformity, a central coordinator has been appointed, who is supervised by a working group of experts in every field of medical genetics. New codes or changes to the existing list can be requested by medical geneticists who use the list to code diagnoses. In order to generate a list that is suitable for genetic registration, it is inevitable that not only diagnoses of recognized genetic disorders but also clinical entities with unknown etiology and developmental defects due to intrauterine infections or maternal exposure to teratogenic agents are included. The purpose is to have a list that can be used for coding diagnoses ranging from

TABLE I. Random Assignment in Uniform Genetic Diagnosis Codes Illustrated by the First 10 Entries

Code	Descriptions	ICD/BPA	MIM
0001	Duchenne muscular dystrophy xl Muscular dystrophy type Duchenne xl[a] Muscular dystrophy pseudohypertrophicprogressive Duchenne type xl[a]	359.10	310200
0002	Down syndrome unspecified Mongolism unspecified[a] Trisomy 21 unspecified[a] Trisomy 21 syndrome unspecified[a]	758.09	
0003	Cleft lip unspecified Cheiloschisis unspecified[a]	749.19	
0004	Cleft lip palate unspecified Cheilognathopalatoschisis unspecified[a]	749.29	
0005	Abdominal wall muscle aplasia	756.72	
0006	Prune belly syndrome ad	756.72	100100
0007	Achondrogenesis unspecified	756.43	
0008	Acrocephalosyndactyly type 1 ad Apert syndrome ad[a]	755.50	101200
0009	Acute leukemia unspecified Leukemia acute unspecified[a]	208.0	
0010	Acute granulocytic leukemia Granulocytic leukemia acute[a] Leukemia acute granulocytic[a]	205.0	

[a]Synonyms of the principal description.

broadly defined entities such as unspecified mental retardation to narrowly defined descriptions such as Prader-Willi syndrome due to uniparental disomy.

Since 1992, all 8 Dutch clinical genetic centers receive quarterly updates of the complete list of codes on diskette. The contents can be downloaded to the local automated registration program and/or printed on paper, in alphabetical order (of both the principal descriptions and the synonyms) and in numerical order of either the ICD/BPA or the MIM code. In this way, searches for patients with a certain disease or disorder can be done by means of the unique new Dutch code, the ICD/BPA or the MIM code. The latter 2 frequently result in a broader category of disorders with more than one specific diagnosis code within the Dutch system. At present, a system is being built to process requests and to assign and distribute new codes in an automated way.

DISCUSSION

Adequate registration of diagnoses of congenital malformations is necessary for various reasons. Preservation of data for future counseling of family members and adjustment of counseling already given, when new diagnostic developments make revisions necessary, is a primary goal of registration. Secondly, providing reproducible and compatible data for medical genetic and genetic epidemiological research is an important factor. Both objectives require accurate, detailed, but also uniform registration. This uniformity cannot be obtained by using the notoriously variable names of the diagnoses (e.g., Down syndrome, trisomy 21, and mongolism are different names for one diagnosis). The most adequate solution is to link principal descriptions and synonyms concerning a specific disorder to one unique code and to develop a set of unique codes for etiologically or clinically different disorders. These codes provide the basis for specifying compatible data between centers.

Neither the ICD/BPA nor the MIM coding system was able to provide a classification that fulfilled all the requirements of the Dutch clinical genetics community. In particular, both classification systems lack sufficient subclassification to distinguish between diagnostically important genetic disorders. In addition, individual subclassification of the ICD/BPA codes has led to loss of uniformity. Furthermore, in 1992 a greatly modified 10th revision of he ICD [ICD-10; World Health Organization, 1992] has been released. Presently, preparations are complete to smoothly introduce the ICD-10 into the Dutch coding system, as soon as the Dutch medical disciplines reach a consensus.

In combination, the ICD/BPA and MIM classifications are clearly an improvement for the registration of individual traits and disorders. However, syndromes which do not have a definable monogenic mode of inheritance cannot sufficiently be distinguished. Also, different genetic mechanisms involving the same single gene, leading to identical phenotypes but with different recurrence risks, cannot be subclassified (e.g., Prader-Willi syndrome as demonstrated in Table II). Furthermore, as noted previously, some disorders with monogenic inheritance cannot be classified adequately using the MIM code because different disorders are assigned the same code.

The new coding system for genetic diagnoses has been designed to make use of the beneficial aspects of both the ICD/BPA and the MIM classification and to add further subdivisions essential for adequate registration of genetic diagnoses. Furthermore, new developments in the field of medical genetics can be constantly introduced into the system without loss of reproducibility. For example, the codes for diagnoses that prove out of date can no longer be assigned. However, the medical geneticist is still able to retrace data on patients for whom this diagnosis was used in the past. Every edition of the diagnosis code-list is recognizable by an edition number, which is registered together with the diagnosis code in every record in the database. For example, the registration of a patient as not having fragile X syndrome in 1985, based on the diagnostic procedures available then, has a different meaning than the same diagnosis defined in 1995. This essential difference is implied by the code edition number registered in each situation. The decentralized but nationwide uniform system also supports privacy protection of registered patients, since it avoids the necessity of a single national clinical genetics registry.

An important result of having a uniform, national genetic diagnosis code system is that it provides a stable foundation to assist health insurance companies in deciding which genetic health care procedures can be funded. International use of this classification can in time result in uniformly registered data in medical genetics. This will create unprecedented opportunities for reliable and optimal statistical and epidemiological analysis.

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TABLE II. Subclassification of Prader-Willi Syndrome

Code	Descriptions	ICD/BPA	MIM
0220	Prader-Willi syndrome inheritance unspecified Prader-Willi Labhart syndrome inheritance unspecified[a]	759.87	176270
2217	Prader-Willi syndrome uniparental disomy Prader-Willi Labhart syndrome uniparental disomy[a]	759.87	176270
2218	Prader-Willi syndrome partial deletion chromosome 15 Prader-Willi Labhart syndrome partial deletion chromosome 15[a]	759.87	176270

[a]Synonyms of the principal description.

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